histidine-histidine-histidine-serine-serine-glycine-leucine-valine-proline-arginine-glycine-serine-proline sequence (SEQ ID NO: 99) at the N-terminus; and

(h) having a glycine-serine-proline sequence at the N-terminus. --

REMARKS

The foregoing amendments and the following remarks are submitted in response to the Office action mailed April 6, 1999.

Status of the Claims

Claims 124 and 132-164 are pending in the application. Claims 54-123, 125-131, 161 and 162 have been canceled, without prejudice. Claims 124, 132-137, 139-143, 145-149 and 155-159 have been amended in order to more particularly point out and distinctly claim that which Applicants regard as the invention. New Claims 165-173 are presented. Support for the amended claims and new claims can be found generally through Applicants' Specification.

The Specification Fully Enables the Claimed Invention

The Examiner has rejected Claims 124 and 132-164 under 35 U.S.C. 112, first paragraph, because the Examiner asserts that "the specification, while being enabling for the use of a gene encoding the OB polypeptide as shown in SEQ ID NOS: 2, 4, 5 or 6 as well as any OB polypeptide thereof lacking the signal sequence of amino acids 1-21, for modulating the body weight of *ob/ob* mice or normal mice, does not reasonably provide enablement for using other variants (except natural alleles), muteins, analogs and fragments of these OB polypeptides, nor is the specification enabling for modulating the body weight of any other mammals, including humans". The Examiner reiterates two specific issues regarding enablement of the scope of the claims, each of which will be addressed by Applicants below.

The first issue presented by the Examiner regarding enablement is based upon his assertion that the Specification fails to enable other variants, analogs or fragments of the OB polypeptide to function as claimed. Applicants respectfully disagree and submit that the Specification provides sufficient guidance and a significant and representative number of such

variants, analogs and fragments- including modifications at any of 22 divergent sites between mouse and human OB polypeptide- capable of modulating body weight to enable the full scope of the claimed genus of sequences encoding OB polypeptide. Applicants note that the Examiner made particular comments in his response, at page 4, which are relevant:

> ... applicant has clearly indicated that these 22 cites [sic, sites] were clearly demonstrable of species differences in the OB protein which ***do not*** affect the characteristics of the OB protein in its ability to affect weight in an *ob/ob* mouse. The skilled artisan could easily be directed to make specific amino acid changes within any or all of these specifc sites and reasonably expect to obtain an protein which would be identifiable both structurally and functionally as an OB protein. In fact, it could be argued that applicant has set forth a comparison of the mouse and human genes and identified the specific sites where specific amino acids may differ, thus demonstrating a "generic mammalian OB protein" which is constant over the 83% of the amino acids found at specific sites. The other remaining sites could vary without affecting the identity of the OB protein.

In an effort to facilitate prosecution, and without prejudice to continued prosecution, Applicants have now amended the claims and present new claims, all of which are particularly directed to use of a gene encoding the OB polypeptide as shown in SEQ ID NOS: 2, 4, 5 or 6, any OB polypeptide thereof lacking the signal sequence of amino acids 1-21, and to particular variants and analogs which incorporate modifications at the 22 divergent sites, all of which are explicitly supported and enabled by the Specification. Applicants point out that the OB polypeptides referred to in the now amended and newly presented method claims parallel those now issued from copending application Serial No. 08/347,563 (U.S. Patent No. 5,935,810) and indicated as free from prior art in copending application Serial No. 08/438,211.

The second issue reiterated and maintained by the Examiner regarding enablement is in regard to the scope of enablement for the methods which modify the body weight of a mammal. The Examiner, in his earlier rejection (Paper No. 17 dated May 21, 1998), using treatment of humans as an example, noted that because the Specification fails to identify the individuals within a population of obese humans who would benefit from administration of a vector encoding the OB protein, the invention cannot be said to be enabled for modulating body weight as broadly claimed. The Examiner further stated in his earlier rejection, at page

11-12, that:

> It is clear from the teachings of the Muzzin et al. reference, cited in the previous office action, that administration of a vector containing the leptin protein will cause a "total correction of the obese phenotype of the *ob/ob* mice." It is also evident from the teachings of Campfield et al., also cited in the previous office action, that not all obese mice will respond to such treatments because the defect causing the obesity lies in a gene other that the that encoding OB protein.

The Examiner further refers to previously cited references which he indicated as teaching that obesity in humans, in particular, is a complex issue, including Sorensen et al. 1995 and Maffei 1996. The Examiner also stated at pages 12-13 of his earlier rejection:

> Given the lack of guidance of the specification on how to affect body changes in humans, the uncertainty in the state of the art as to the complex causes of obesity in humans, the unpredictability of gene therapeutics in general in the art and the lack of any current art recognized genetic alterations of body weight in humans, it would require undue experimentation to practice the invention for its scope.

Applicants do not deny that the cited references indicate that obesity in humans can be due to defects other than in the *OB* gene or its encoded polypeptide, however Applicants do respectfully submit that it would not constitute undue experimentation to identify the individuals within a population of obese humans who would benefit from administration of a vector encoding the OB protein and/or to test OB gene therapy methods of modifying body weight in these obese humans. In particular, the teachings of the Specification and those cited by the Examiner himself provide significant guidance for the skilled artisan and reduce the uncertainty and unpredictability of the art to the level such that undue experimentation is not required. In fact, the instant Application and Applicants' discovery of the *OB* gene and its encoded polypeptide in mice and humans (as well as identification of homologous sequences in other mammals, including rats, rabbits, sheep, cows, pigs and chickens) provided the answer to a long sought question of identification of an art recognized genetic alteration of body weight in mice, also likely to be relevant in humans and other mammals. While not all obesity in humans is necessarily related to alterations in the *OB* gene or its encoded peptide, in fact,

some of obesity is so related and has been readily tested and demonstrated as such, by the skilled artisan, without undue experimentation. Further, Applicants respectfully submit that the law does not require that the Specification enable the treatment of all obese patients. As Applicants have before stated, the skilled artisan can, using diagnostic methods known in the art and the teaching in the Specification, including at page 65-69, identify those individuals, including those with altered or unaltered levels or forms of OB polypeptide, which could reasonably be expected to benefit from the administration of the OB gene (or polypeptide) to modify body weight as claimed. The skilled artisan authors of the Examiner's cited reference of Maffei et al were able to test, without undue experimentation and using methods including those described in the Specification, individuals within a population of obese humans to determine whether they had an alteration in the open reading frame of the OB protein.

The Applicants also acknowledge that while environment plays a role, its role is conditional on a given genetic background. This genetic background, and the susceptibility of that genetic background to OB gene therapy methods, Applicants argue, using the methods disclosed in the present Specification, is readily evaluated by the skilled artisan without undue experimentation.

Applicants respectfully assert that methods of gene therapy for weight modulation are enabled for the skilled artisan. Gene therapy has attained significant clinical application and, while necessitating some experimentation, including appropriate clinical evaluation, has been shown to be a feasible treatment modality for a variety of ailments, including particularly OB gene therapy for treatment of obesity. By way of a specific example, Applicant's point to references cited by the Examiner, particularly Fletcher et al. (1996), Fletcher et al. (1995), Muzzin et al. (1996) and Campfield et al. (1995) which discuss studies demonstrating the efficacy of *OB* gene therapy *in vivo*. In Fletcher et al. (1996) the authors report the results of retroviral vector-mediated expression of soluble leptin in mice. Importantly, Fletcher et al. (1996) demonstrates gene therapy to modify body weight in both wild-type and obese animals, finding that chronic expression of normal, unmutated leptin resulted in reduction of body weight, even in animals already expressing normal (wild-type) or mutated (*ob/ob*) leptin. The Fletcher et al. (1995) abstract reports on *ex vivo* manipulation of *ob/ob* bone marrow by

transduction with wild-type *OB* cDNA. In concluding, this reference states that:

> ... these data demonstrate the feasibility of gene replacement therapy for the treatment of obesity and provide a basis for further investigations.

Similarly, Muzzin et al reports correction of obesity and diabetes in genetically obese *ob/ob* mice by leptin gene therapy. Treatment of the *ob/ob* mouse with a recombinant adenovirus expressing the mouse leptin cDNA resulted in dramatic reductions in both food intake and body weight, as well as the normalization of serum insulin levels and glucose tolerance. Campfield et al report that administration of recombinant OB protein reduced food intake and body weight of *ob/ob* mice, diet-induced obese mice and lean mice, but not of *db/db* obese mice. These authors note, at page 548, that the failure to observe a reduction in *db/db* mice

> is consistent with the hypothesis that the genetic defect in *db/db* mice renders them unable to appropriately respond to OB protein, perhaps because of a defect in the OB protein receptor or the postreceptor signaling pathway.

This hypothesis has subsequently been shown to be true, with the *DB* gene now identified as encoding the OB polypeptide receptor. That *db/db* mice have increased levels of OB mRNA and do not respond to administration of OB polypeptide was demonstrated by Applicants, including in the Specification at page 98 and in Example 8, as detailed on page 114, lines 24-26. Based on this teaching in the Specification and his concurrent knowledge, the skilled artisan would have predicted that gene therapy methods of administration of OB polypeptide alone would not modify or correct *db/db* obesity. Applicants point out that, similar to diagnostic methods for OB, the skilled artisan can now readily identify those individuals with altered or unaltered levels or forms of DB polypeptide. These references clearly confirm the feasibility of *OB* gene therapy methods to modify body weight in mice, humans and other mammals, as taught by the Specification, and confirm that the gene therapy aspects of the present invention are enabled and can be practiced by the skilled artisan without undue experimentation.

With regard to Claims 161 and 162, the Examiner argues that the Specification fails to describe or teach how to make and/or use the invention claimed. Applicants again assert that the skilled artisan could, using the present Specification, practice such claimed methods and

could insert an expression regulatory control sequence in functional proximity to OB polypeptide encoding sequence or administer mammalian cells comprising an OB polypeptide encoding sequence modified *in vitro* by such means. Nonetheless, in an effort to facilitate allowance, and without prejudice to continued prosecution, Applicants have canceled Claim 161 and 162.

In view of the foregoing remarks, Applicants submit that the Examiner's rejection under 35 U.S.C. 112, first paragraph, may properly be withdrawn.

Particularity and Distinctiveness of the Claims

The Examiner has rejected Claims 133, 141, 147, 157 and 164 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention.

Regarding Claims 133, 141, 147 and 157, the Examiner comments that the term " identity" is vague and indefinite and that the Specification fails to set forth its meaning. Applicants respectfully disagree. The skilled artisan will understand and can readily determine those amino acids which are identical, particularly in light of the teaching in the Specification. Clarification, meaning and support for the term "amino acid identity" is found in the comparison of the disclosed amino acid sequences of mouse and human OB polypeptides. Specifically the Specification characterizes the percentage (%) identity between the mouse and human OB amino acid sequences, where at page 12, lines 20-21, the Specification now states that

> Overall, there is 83% identity at the amino acid level, ...

and at page 102, lines 15-17, the Specification now states that

> Comparison of the human and mouse ob polypeptide sequences showed that the two molecules share an overall 83% identity at the amino acid level (Figure 4).

Figure 4, which provides a comparison of the mouse and human amino acid sequences aligned with one another, demonstrates that there are 28 amino acid differences between the human and mouse sequences, out of a total of 167 amino acids. Thus, 139 amino acids, or 83%, are

identical, i.e. Alanine for Alanine, Glutamine for Glutamine. It is believed to be particularly straightforward for the skilled artisan to make such a comparison since the length of the mouse and human OB polypeptides are the same and the corresponding amino acids to compare in assessing identity is very readily determined - no gaps exist and no accounting for regions of extra amino acids is necessary. In addition, the skilled artisan's comparison of SEQ ID NO: 5 (which is the mouse variant OB polypeptide with glutamine 49 deleted) with SEQ ID NO:6 (which is the human variant OB polypeptide with glutamine 49 deleted) will yield the same result of 83% amino acid identity in a similarly straightforward fashion.

With regard to Claim 164, the Examiner asserts that the Specification fails to teach what is "moderate stringency hybridization condition". Applicants respectfully disagree and point out that the Specification clearly teaches what is moderate stringency hybridization condition, including at pages 44-45, where hybridization conditions are particularly discussed and specifically elaborated. Applicants further point out that Claim 164 also requires that any such hybridizing nucleic acid molecule have an important and specific additional functional characteristic in that it must encode an OB polypeptide "capable of modulating body weight".

In view of the foregoing remarks, Applicants request that the Examiner's rejection be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Should the Examiner feel that further issues remain upon a review

of this response, he is invited to call the undersigned at the number listed below to effect their resolution. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,

KLAUBER & JACKSON

Christine E. Dietzel, Ph.D.
Agent for Applicant(s)
Registration No. 37,309

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack NJ 07601
Tel: (201) 487-5800